TABLE 22. Pulmonary hemorrhages at any time by birth weight.- Number/total (percentage) of patients.

	ITT	TBW	<700 g	>1350 g
Infasurf	27/570 (4.7)	19/190 (10)	8/36 (22)	0 (0)
Exosurf	28/556 (5)	18/210 (8.5)	6/34 (17.6)	4/309 (1.3)
p-value	.90	.73	.77	

*Fisher's two-tailed test

(5) Severity of BPD

The severity of BPD was determined from the type of respiratory support required at 28 days post-birth and 36 weeks PCA. There was no significant difference between treatment groups in the distribution of BPD/chronic lung disease severity as related to the type or amount of oxygen supplementation required at either 28 days or 36 weeks PCA for either the ITT or TBW populations. Table 23 shows the distribution of the respiratory support received per treatment group at 28 days, Table 24 presents the data at 36 weeks PCA.

TABLE 23. Respiratory Requirements at 28 days - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=523)	Exosurf (N=498)	p-Value Distributional	Infasurf (N=168)	Exosurf (N=180)	p-Value Distributional
Ventilated	74 (14.1)	84 (16.9)	0.37	55 (32.7)	57 (31.7)	0.62
CPAP	21 (4.0)	11 (2.2)		15 (8.9)	10 (5.6)	
Hood Oxygen	8 (1.5)	10 (2.0)		5 (3.0)	9 (5.0)	
Nasal Cannula	75 (14.3)	71 (14.3)		39 (23.2)	40 (22.2)	
Room Air	345 (66.0)	321 (64.5)		54(32.1)	64 (35.6)	
Unknown	0 (0.0)	1 (0.2)		0 (0.0)	0 (0.0)	

Cross Reference: Data Listing 9 of Case Report Tabulations (NDA Section XI)

TABLE 24. Respiratory Requirements at 36 weeks PCA - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=521)	Exosurf (N=493)	p-Value Distributional	Infasurf (N=166)	Exosurf (N=177)	p-Value Distributional
Ventilated	31 (6.0)	33 (6.7)	0.23	12 (7.2)	14 (7.9)	0.24
CPAP	14 (2.7)	4 (0.8)		7 (4.2)	2 (1.1)	
Hood Oxygen	8 (1.5)	9 (1.8)		2 (1.2)	6 (3.4)	
Nasal Cannula	91 (17.5)	88 (17.8)		52 (31.3)	47 (26.6)	
Room Air	325 (62.4)	327 (66.3)		93 (56.0)	107 (60.5)	
Unknown	0 (0.0)	3 (0.6)		0 (0.0)	1 (0.6)	

Cross Reference: Data Listing 9 of Case Report Tabulations (NDA Section XI)

D. Safety Results

(1) Incidence and Severity of IVH

The incidence and severity of IVH was determined from brain sonograms read by the radiologist at each study site.

Brain sonograms were scheduled at 3-7 days and 4-8 weeks and read by the radiologist at each study site to detect IVH and PVL. If no lesion was detected on sonograms available, the patient was reported as having no IVH or PVL.

In the ITT population, significantly fewer (p=0.01) Infasurf-treated patients developed IVH only (21.3%) than did Exosurf-treated infants (28.0%); within the TBW population, the two treatment groups were comparable. In the ITT and TBW populations, between treatment group comparisons showed there were no significant between treatment group differences in the identification of PVL only. The incidence of patients with both PVL and IVH, within the ITT population, was significantly less (p=0.04) in the Exosurf treatment group (2%) than in the Infasurf treatment group (5%); within the TBW population, there was no significant difference between the treatment groups. When patients with IVH, PVL, or both were combined and analyzed, no significant between treatment

group differences were noted within the ITT or TBW populations. There were no significant differences between treatment groups in the distribution of IVH grades in either the ITT or TBW populations.

TABLE 25 presents the number (percentage) of infants in each treatment group who developed IVH only, PVL only, both PVL and IVH; IVH, PVL or both, and the distribution of IVH severity. The data are presented for the ITT population and for the TBW population. Table 26 shows such analysis for the under 700 grams and over 1350 grams birth weight.

TABLE 25. Incidence of IVH, PVL, PVL and IVH, Combined Incidence, and Severity Grade of IVH - as Determined at Study Sites - Number (Percentage) of Patients - ITT and TBW Populations.

Parameter	ITT Population (N=1033)			TBW Population (700-1350 g) (N=382)		
	Infasurf (N=526)	Exosurf (N=507)	p-Value	Infasurf (N=184)	Exosurf (N=198)	p-Value
IVH only*	112 (21.3)	142 (28.0)	0.01[1]	54 (29.3)	72 (36.4)	0.17[1]
PVL only*	14 (2.7)	11 (2.2)	0.69	7 (3.8)	5 (2.5)	0.56
PVL and IVH*	25 (4.8)	12 (2.4)	0.04	13 (7.1)	8 (4.0)	0.26
PVL, IVH, or both*	151 (28.7)	165 (32.5)	0.17[1]	74 (40.2)	85 (42.9)	0.64[1]
IVH Grade •	Infasurf (N=136)†	Exosurf (N=154)		Infasurf (N=67)	Exosurf (N=80)	
I	62 (45.6)	80 (51.9)		26 (38.8)	34 (42.5)	
II	24 (17.6)	29 (18.8)		12 (17.9)	16 (20.0)	
III	36 (26.5)	22 (14.3)		21 (31.3)	14 (17.5)	
IV	14 (10.3)	23 (14.9)		8 (11.9)	16 (20.0)	
Distributional p-Value	p = 0.07			p = 0.21		

*Denominator is the number of infants with either an IVH or PVL determination
[1] Based on logistic regression model
• By readers at individual centers
I = Subependymal hemorrhage
II = Intraventricular, no acute ventricular dilatation
III = Intraventricular, with acute ventricular dilatation
IV = Intraparenchymal
† - One patient had no recorded IVH grade.
Cross Reference: Data Listing 13 and 14 of Case Report Tabulations (NDA Section XI)

TABLE 26. Incidence of IVH, PVL, and both Combined Incidence, and Severity of IVH - as Determined at Study Sites - Number (Percentage) of Patients -Birth Weight Populations < 700 g and > 1350 g

Parameter	Birth Weight Population: < 700 g (N=58)			Birth Weight Population: > 1350 g (N=593)		
	Infasurf (N=28)	Exosurf (N=30)	p-Value	Infasurf (N=314)	Exosurf (N=279)	p-Value
IVH only*	11 (39.3)	17 (56.7)	0.29[1]	47 (15.0)	53 (19.0)	0.20[1]
PVL only*	1 (3.6)	1 (3.3)	1.00	6 (1.9)	5 (1.8)	1.00
PVL and IVH*	4 (14.3)	3 (10.0)	0.70	8 (2.6)	1 (0.4)	0.04
PVL, IVH, or both*	16 (57.1)	21 (70.0)	0.39[1]	61 (19.4)	59 (21.2)	0.58[1]
IVH Grade *	Infasurf (N=15)	Exosurf (N=20)		Infasurf (N=54)†	Exosurf (N=54)	
I	2 (13.3)	6 (30.0)		34 (63.0)	40 (74.1)	
II	3 (20.0)	4 (20.0)		9 (16.7)	9 (16.7)	
III	8 (53.3)	5 (25.0)		7 (13.0)	3 (5.6)	
IV	2 (13.3)	5 (25.0)		4 (7.4)	2 (3.7)	
Distributional p-Value	p = 0.35			p = 0.52		

* Denominator is the number of infants with either an IVH or PVL determination
[1] Based on logistic regression model
* By readers at individual centers
I = Subependymal hemorrhage II = Intraventricular, no acute ventricular dilatation
III = Intraventricular, with acute ventricular dilatation IV = Intraparenchymal
† One patient had no recorded IVH grade.
Cross Reference: Data Listing 13 and 14 of Case Report Tabulations (NDA Section XI)

When comparing the two treatment groups in terms of poor acute outcomes, i.e., patients with severe IVH (grades III and IV), PVL or patients who died, it was found that no statistical significance was reached in any of the birth weight subsets. Table 27 presents patients in the ITT and the TBW populations with poor acute outcomes, and those who survived without PVL or severe IVH.

TABLE 27. **Poor Acute Outcomes: Patients Who Died or Survived with PVL and/or Severe IVH - Number (Percentage) of Patients - ITT and TBW Populations**

Severe IVH*, PVL and/or Death	ITT Population (N=1126)		TBW Population (700 - 1350 g) (N=403)	
	Infasurf (N=570)	Exosurf (N=556)	Infasurf (N=190)	Exosurf (N=213)
Died, or Survived with PVL and/or Severe IVH	109 (19.1)	113 (20.3)	56 (29.5)	69 (32.4)
Survived without PVL or Severe IVH	461 (80.9)	443 (79.7)	134 (70.5)	144 (67.6)
Distributional p-Value	p = 0.58[1]		p = 0.59[1]	

* Severe IVH is defined as grade III or IV on study site evaluation.
[1] Based on logistic regression model.
Cross Reference: Data Listing 7, 13 and 14 of Case Report Tabulations (NDA Section XI)

Reviewer's note: The Infasurf group again had statistically significantly more cases of PVL and IVH in the ITT than the Exosurf group. In this trial, however, Exosurf had statistically significantly (p=0.01) more IVH cases than the Infasurf treatment group. For those sonograms centrally read at the coordinating study center, the analysis yielded about the same results as when analyzed at the study sites except that significantly fewer Exosurf-treated patients than Infasurf-treated patients were identified with IVH, PVL, or both within the ITT population (Infasurf 40.9%, Exosurf 33.3%; p=0.03) and the TBW population (Infasurf 41.7%, Exosurf 30.4%; p=0.01). The data was then analyzed in terms of poor outcome, i.e., patients who died or were alive but with severe IVH (grades III or IV) or PVL. Regardless of where the determinations were made, within both the ITT and TBW populations, there was no significant difference between treatment groups in the distribution of those patients with poor outcomes (those who died, or survived but had PVL and/or severe IVH), and those with positive outcomes (i.e., who survived without PVL or severe IVH).

(2) Complications of Prematurity

The complications of prematurity included: retinopathy of prematurity (ROP), posthemorrhagic hydrocephalus (PHHC), necrotizing enterocolitis (NEC), and patent ductus arteriosus (PDA). For all complications evaluated, the between treatment group comparisons show the incidences to be similar in the Infasurf-treated and Exosurf-treated infants.

(3) Adverse Events

If any of the following occurred in association with surfactant administration they were recorded as adverse events.

Bradycardia	**Sustained decrease in heart rate < 100 during surfactant administration, air leak, or loss of the endotracheal tube requiring intervention (e.g., increased peak inspiratory pressure or intermittent mandatory ventilation, increased fraction of inspired oxygen , thoracentesis, or reintubation).**
Airway obstruction	**Clinical diagnosis; must require and respond to intervention (increased peak inspiratory pressure, suctioning, or reintubation).**
Reflux	**Surfactant reflux through the mouth or nares after delivery of surfactant through the endotracheal tube.**
Cyanosis	**Onset or increase in cyanosis during surfactant administration that requires intervention (as under bradycardia).**

The between treatment group comparisons showed more adverse events associated with Infasurf administration than with Exosurf. Among all patients, 72% of Infasurf-treated neonates (411 of 570) and 64% of Exosurf-treated neonates (358 of 556) experienced at least one complication (p=0.006) during first or second dose of therapy.

TABLE 28 presents the incidence of adverse events reported over the course of treatment for patients in both treatment groups in the ITT and TBW populations.

TABLE 28. Total Adverse Events - Number (Percentage) of Patients - ITT and TBW Populations

Parameter	ITT Population (N=1126)			TBW Population (700-1350 g) (N=403)		
	Infasurf (N=570)	Exosurf (N=556)	p-Value	Infasurf (N=190)	Exosurf (N=213)	p-Value
Bradycardia	131 (23.0)	56 (10.1)	<0.001	53 (27.9)	29 (13.6)	<0.001
Airway Obstruction	145 (25.4)	64 (11.5)	<0.001	52 (27.4)	22 (10.3)	<0.001
Reflux	120 (21.1)	101 (18.2)	0.23	42 (22.1)	30 (14.1)	0.04
Cyanosis	332 (58.3)	280 (50.4)	0.008	113 (59.5)	102 (47.9)	0.02
Reintubation	13 (2.3)	2 (0.4)	0.007	3 (1.6)	1 (0.5)	0.35
Manual Ventilation	58 (10.2)	23 (4.1)	<0.001	21 (11.1)	7 (3.3)	0.003
Any	411(72.1)	358 (64.4)	0.006	140 (73.7)	134 (62.9)	0.03

Cross Reference: Data Listing 15 of Case Report Tabulations (NDA Section XI)

Reviewer's note: There is an increase in AE's with the administration of Infasurf. The sponsor claims that the statistically significant increase in adverse events during the administration of the second dose, not seen during the administration of the first dose (data not presented here), is because of the lower levels of FiO2 that the infants on Infasurf were receiving at the time of the second dose. The sponsor attempted to explain this phenomenon for various variables like FiO2, MAP, etc. to demonstrate an association between some ventilatory variables and the occurrence of the adverse events. The model fit is

FiO2 = Treatment + Bradycardia + Treatment x Bradycardia

The statistical model used by the sponsor failed to demonstrate such a relationship consistently in the treatment trial. In addition, the validity of the model is questionable since bradycardia, cyanosis, and airway obstruction are outcomes of the study and not predictors.

10. Summary

In the Treatment Trial, 570 premature infants were treated for RDS with Infasurf and 556 premature infants were treated with Exosurf.

Infants in the Exosurf group were slightly lighter than infants randomized to receive Infasurf (1564 g vs. 1648 g; p=0.04) and had a slightly younger gestational age (30.6 weeks vs. 31.0 weeks; p=0.02). The clinical significance of these differences can be questioned, specially the difference in gestational age.

Obstetrical demographics between treatment groups were, in general, similar.

Most infants in both treatment groups presented for surfactant therapy with moderate RDS, i.e., 57% of the infants randomized to receive Infasurf and 55% of the infants randomized to receive Exosurf. The overall distribution of RDS severity at entry was similar between both treatment groups (p=0.85).

Results that Support the Approval of Infasurf.
Infasurf showed a statistically significant superiority over Exosurf on the primary efficacy endpoint, air leaks. Pneumothorax and pulmonary interstitial emphysema, when assessed individually, were also documented in statistically significantly fewer Infasurf-treated infants than Exosurf-treated infants.

There was a tendency of improved survival to discharge in the Infasurf-treated group than in the Exosurf-treated group (p=0.07). The 95% confidence intervals of the difference between Infasurf and Exosurf on total neonatal mortality, (-0.069, 0.003) indicate with high confidence that Infasurf can be as much as 7% better or as much as 0.3% worse than Exosurf on this endpoint.

Results That Do Not Support the Approval of Infasurf.
The Infasurf group was statistically significantly worse in the incidence of PVL and IVH combined in the ITT population than the Exosurf group. When the two treatment groups were compared in terms of having poor prognosis (those patients who died or had PVL or severe IVH) vs. good prognosis (patients who survived without PVL or severe IVH), Infasurf showed comparable results). Infasurf also showed a statistically significant increase in adverse events, i.e., bradycardia, cyanosis, and endotracheal obstruction, during its administration, as seen in the prophylaxis trial.

Other Results
Infasurf and Exosurf were comparable in total mortality as discussed above; total respiratory mortality (95% CI of the difference are -0.053,

0.0038 as assigned by the study sites and -0.042, 0.014 by the committee); RDS related mortality (95% CI = -0.039, 0.008 study sites, -0.024, 0.022 committee) and incidence of BPD. Infasurf did not seem to increase in this study the incidence of the most common complications of prematurity (PDA, ROP, PHHC, and NEC) or pulmonary hemorrhage, seen in both treatment groups.

11. Discussion and Conclusions

The SCT-T trial showed that Infasurf was more effective than Exosurf in the treatment of RDS in premature infants by reducing more pulmonary air leaks as complications of RDS in premature infants, and by showing a comparable effect on total neonatal mortality, total respiratory mortality and mortality due to RDS, clinically relevant parameters on which Exosurf consistently demonstrated its superiority to placebo in its pivotal studies. Infasurf and Exosurf had similar incidence of BPD. This finding agrees with other trials published in the literature, where surfactants in general have not consistently made an impact in the incidence of BPD.

Due to the nature of the disease studied, the safety profile includes the parameters discussed above (total mortality, mortality by cause, and air leaks) . Besides these major variables, on which Infasurf demonstrated to have lower/comparable incidence when compared to Exosurf, Infasurf did show an increased incidence on two parameters: 1) intracranial hemorrhages, also found in the prophylaxis study, and as discussed before, the phenomenon will be further discussed with the Advisory Committee panel to determine its implication in the overall safety of the drug; and 2) AE's (bradycardia, cyanosis, airway obstruction, reintubation and manual ventilation) with the administration of Infasurf. The reason for the increase in the incidence of these adverse events during the administration of Infasurf is not clear, but these findings were consistently present in all the controlled trials. Even though the AE's were reported as transient and with no further consequences to the patients after their resolution, they should be properly addressed in the label.

III. Comparison of Natural Surfactants In the Prevention (CNS-P) and Treatment (CNS-T) of Respiratory Distress Syndrome

1. **Principal Investigator:** Barry T. Bloom, MD, University of Kansas - Wichita

2. **Objective:** Compare Infasurf to Survanta (Beractant), in efficacy and safety for prophylaxis and treatment of RDS in premature infants.

3. **Study Design:** A multicenter, prospective, randomized, masked, multidose, active treatment concurrent control (Survanta) study with two arms: prophylaxis for RDS and treatment of RDS.

4. **Study Size:**
   - Prophylaxis: Infasurf = 227; Survanta = 236
   - Treatment: Infasurf = 329; Survanta = 333

5. **Inclusion Criteria:**
   - Prophylaxis: Inborn, ≤30 weeks gestation, ≤1250 grams birth weight, without major anomaly, without congenital sepsis.
   - Treatment: X-ray diagnosis of RDS, a/A PO2 ≤0.22, <2000 grams birth weight, < 48 hours of age, without congenital sepsis.

6. **Dosage:** Survanta 4 ml/kg of 25 mg/ml suspension
   Infasurf 4 ml/kg of 25 mg/ml suspension.

Reviewer's note: Infasurf had 25 mg/ml of phospholipids, the proposed concentration for marketing is 35 mg/ml.

7. **Administration:** **Both drugs were administered following the instructions in the package insert for Survanta: through a 5 French feeding tube inserted in the endotracheal tube. The total dose was given in four aliquots with the patient in 4 different positions. Repeat doses were administered before 96 hours of age, when more than 6 hours had elapsed since the previous dose and the patient was on ≥30% oxygen for RDS with a PaO_2 <80, or had an a/A PO_2 <0.33. A maximum of 4 doses was required in the protocol. If there was still on-going respiratory disease after four doses, the patient's physician could administer additional dose(s) of the study surfactant or cross over the patient to the other surfactant.**

8. **Efficacy Endpoints:**
   - **A. Intact cardiopulmonary survival**
   - **B. Incidence of RDS (Prophylaxis arm only)**
   - **C. Severity of RDS: as measured by need for retreatment, respiratory support requirements and incidence of pulmonary complications of RDS.**

Reviewer's note: The endpoints in the protocol were not specified as primary or secondary. Intact cardiopulmonary survival was retrospectively defined as primary.

9. **Safety Endpoints:**
   - **A. Incidence of serious complications of prematurity**
   - **B. Adverse events at dosing**
   - **C. Unexpected adverse events**

10. **Statistical Analysis:**

Study Size **CNS-P** **A study with 80% power and an alpha error of .05 to show that Infasurf reduced the Survanta rate of two or more doses by 15% or more (Survanta' s two dose rate = 60%) required a total of 372 evaluable patients.**

CNS-T	**It was originally calculated that a study with 80% power and a 5% false positive rate to show that Infasurf reduced the 64% Survanta rate of three or more doses to 46% or less would require 320 evaluable patients. However early in the study it was observed that the overall expected rate of three or more doses had been overestimated, so a new study size was calculated with the same power and sensitivity and the assumption that the Infasurf rate would be 3/4 ths or less of the Survanta rate when the Survanta rate was 56%. A new study size of 600 evaluable patients was determined.**

Reviewer's note: The sponsor did not unblind the treatment groups when they did the reestimation of the sample size. No interim analysis was performed either.

11. Results

Intent-to-treat population.
In the prophylaxis trial, 227 patients were randomized to receive Infasurf, and 236 patients to receive Survanta. In each treatment group, 3 patients never received surfactant treatment. This left the Intent-to-treat (ITT) population with 224 subjects in the Infasurf group, and 233 subjects in the Survanta group.

In the treatment arm, 331 and 334 patients were randomized to receive Infasurf and Survanta respectively. Two patients in the Infasurf group and 1 patient in the Survanta group were never treated. Therefore, the ITT population consisted of 329 and 333 patients in the Infasurf and Survanta groups, respectively.

Post Randomization Exclusions: Evaluable Population.
Prospectively, the protocol identified certain congenital anomalies which would prevent invitation to enroll, if present. The Data Monitoring and Advisory Committee (DM&AC) decided on a case-by-case basis to include or exclude patients whose anomalies were only diagnosed after randomization. The DM&AC decided that all patients randomized with congenital anomalies or pre-existing

conditions which would have excluded them if known before randomization should all be excluded and not reviewed individually. In addition, infants accidentally enrolled who exceeded the weight limitation, outborn infants wrongly enrolled in the prophylaxis trial and "major" protocol deviations were proposed to be excluded from the primary analysis by the Study Chairman, and that decision was approved by the DM&AC. "Major" protocol deviations were:

- **Failure to give dose #1 in CNS-P at birth; in CNS-T within 12 hours of qualifying.**
- **Failure to give dose #2 within 8 hours of being indicated in both CNS-P and CNS-T**
- **Failure to give indicated dose #3 in CNS-T**
- **Retreated by error with wrong drug**
- **Retreated without meeting FIO2 criteria**

Target Birth weight (TBW) population
Includes patients within the evaluable population with a birth weight of 600 - 1250 grams. This subset was extracted post hoc from the data base to provide a subset that parallels the patient population profile of the original Survanta placebo controlled treatment trial.

Reviewer's note: The distribution of and the causes for the exclusion of patients from the randomized and treated population (ITT) is shown in TABLE 1. It is unknown whether these patients were excluded in an unblinded manner or after an initial analysis of the data had been done. In addition, the protocol did not specify some of the criteria that were later used as basis for exclusion of patients, i.e., the maximum period allowed to administer the initial dose after qualifying, or a repeat dose (after the required 6 hours post last dose of surfactant) once it was indicated.

TABLE 1. Patients excluded from the ITT population by arm and treatment drug. Number of patients.

	Prophylaxis arm			Treatment arm		
Exclusions	Infasurf (N=224)	Survanta (N=233)	p-value	Infasurf (N=329)	Survanta (N=333)	p-value
Outborn Infant/not eligible	10	3		0	3	
Birth weight above criterion[1]	5	12		3	0	
Congenital anomaly	3	2		3	1	
Hydrops	0	1		1	1	
Congenital sepsis	14	10		10	15	
Major protocol deviations	12	11		9	8	
Evaluable population	180	194	0.09[2]	303	305	0.32[2]

[1]>1250 grams for the Prophylaxis arm, and > 2000 grams for the Treatment arm.
[2]Distribution p-value.

A. Demographics

Patients in the Prophylaxis arm showed a statistically significant increase in mean birth weight in favor of Infasurf in the evaluable population (p=0.04). This difference was not seen in the randomized and treated population (ITT population). In the Treatment arm, there were no statistically significant differences in the demographics of both treatment groups in the ITT or in the evaluable population. TABLES 2 and 3 show the demographic characteristics of the prophylaxis and the treatment trials respectively.

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TABLE 2. Demographic characteristics. Prophylaxis Arm.

DEMOGRAPHIC VARIABLES	TREATED POPULATION Infasurf (N=224)	Survanta (N=233)	p-value	EVALUABLE POPULATION ≤1250 grams Infasurf (N=180)	Survanta (N=194)	p-value	EVALUABLE TBW POPULATION 600-1250 grams Infasurf (N=158)	Survanta (N=172)	p-value
Birth Weight (g)[a]	886 ± 234	876 ± 238	0.73	891 ± 221	845 ± 205	0.04	941 ± 186	889 ± 174	0.01
Gestational Age (wks)[a]	26.3 ± 1.8	26.3 ± 1.8	0.98	26.4 ± 1.8	26.1 ± 1.7	0.27	26.6 ± 1.7	26.4 ± 1.6	0.28
Sex, Males	117(52)	113(49)	0.46	95(53)	90(46)	0.26	89(56)	87(51)	0.32
Race, White	103(46)	101(43)	0.57	82(46)	78(40)	0.35	72(46)	67(39)	0.26
Singleton Births	176(79)	195(84)	0.19	142(79)	164(85)	0.18	123(78)	143(83)	0.27
SGA[b]	29(13)	23(10)	0.31	21(12)	20(10)	0.74	13(8)	13(8)	0.84

[a] All quantitative values given as mean ± Standard Deviation
[b] SGA is small for gestational age, less than the 10th percentile by convention.
Cross Reference: Data Listings 2, 3 in Appendix

TABLE 3. Demographic characteristics. Treatment Arm.

DEMOGRAPHIC VARIABLES	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value	EVALUABLE TBW POPULATION Infasurf (N=251)	Survanta (N=260)	p-value
Birth Weight (g)[a]	1,171 ± 414	1,165 ± 402	0.86	1,162 ± 408	1,166 ± 401	0.92	1,130 ± 320	1,115 ± 323	0.61
Gestational Age (wks)[a]	28.3 ± 3.0	28.2 ± 2.9	0.68	28.3 ± 2.9	28.2 ± 2.9	0.80	28.2 ± 2.5	28.0 ± 2.6	0.56
Sex, Males	189(57)	191(57)	1.00	173(57)	176(58)	0.94	146(58)	146(56)	0.66
Race, White	165(50)	159(48)	0.59	154(51)	145(48)	0.47	118(47)	120(46)	0.86
Singleton Births	247(75)	257(77)	0.58	225(74)	238(78)	0.30	185(74)	199(77)	0.48
SGA[b]	39(12)	36(11)	0.57	37(12)	32(10)	0.69	31(12)	27(10)	0.79

[a] All quantitative values given as mean ± Standard Deviation
[b] SGA is small for gestational age, less than the 10th percentile by convention.
Cross Reference: Data Listings 15, 16 in Appendix

Reviewer's note: In the Prophylaxis arm there were no statistically significant differences between the surfactant groups in regard to prenatal steroid therapy, endogenous surfactant detected in amniotic fluid and APGAR scores at 1 and 5 minutes in the ITT and the evaluable populations. In the Treatment arm, more Infasurf patients received "any" steroids prenatally in the ITT population, this difference was not statistically significant in the evaluable population. (Even when any prenatal steroid may decrease the incidence and the severity of RDS, both surfactant groups presented similar degree of RDS severity at randomization). Reference: Data listings 2, 3 in Appendix.

B. Efficacy Outcomes

(1) Intact Cardiopulmonary (CP) Survival

This outcome is the number of enrolled patients who survived to 28 days or 36 weeks post-conceptional age without chronic lung disease.

There was no statistically significant difference in the intact CP Survival between the two surfactant groups, in either arm in the ITT and the evaluable population. TABLE 4 shows intact CP survival in the ITT, evaluable and evaluable TBW populations in the Prophylaxis arm. TABLE 5 shows same analysis in the Treatment arm.

TABLE 4. Intact Cardiopulmonary Survival. Prophylaxis arm. Number (percentage) of patients.

INTACT C-P SURVIVAL	ITT POPULATION			EVALUABLE POPULATION			EVALUABLE TBW POPULATION		
	Infasurf (N=224)	Survanta (N=233)	p-value	Infasurf (N=180)	Survanta (N=194)	p-value	Infasurf (N=158)	Survanta (N=172)	p-value
Alive at 28 days, FIO_2 ≤30%	114(51)	138(59)	0.08	96(53)	116(60)	0.21	93(58)	114(66)	0.17
Alive at 36 wks PCA, no O_2	140(63)	157(67)	0.28	120(67)	134(69)	0.66	114(72)	128(74)	0.71

References: data listings 5, 6 in Appendix.

TABLE 5. Intact CP survival in the Treatment arm. Number (percentage) of patients.

INTACT C-P SURVIVAL	ITT POPULATION			EVALUABLE POPULATION			EVALUABLE TBW POPULATION		
	Infasurf (N=329)	Survanta (N=333)	p-value	Infasurf (N=303)	Survanta (N=305)	p-value	Infasurf (N=251)	Survanta (N=260)	p-value
Alive at 28 days, FIO_2 ≤30%	221(67)	206(62)	0.17	208(69)	190(62)	0.11	176(70)	159(61)	0.04
Alive at 36 wks PCA, no O_2	206(63)	199(60)	0.47	192(63)	181(59)	0.32	163(65)	152(58)	0.15

References: data listings 18, 19 in Appendix.

Reviewer's note: In the ITT population of the Prophylaxis arm, intact CP survival showed a trend favoring Survanta at 28 days (p=.08). The difference was less obvious at 36 weeks PCA. See reviewer's comments on mortality below. In the ITT population of the Treatment arm there was no statistically significant difference between both surfactant groups.

(2) Mortality

All deaths that occurred during the hospital stay were included.

Deaths were separated into respiratory and non-respiratory. RDS, chronic lung disease and direct complications of these diseases were the causes of death categorized as respiratory.

All deaths that were not categorized as respiratory were reported as non-respiratory.

In the Prophylaxis trial, in the ITT population, total mortality and respiratory deaths were statistically significantly lower in the Survanta treated population than in the Infasurf treated population (11% versus 18%, p=0.03 and 4% vs 11%, p=0.005, respectively). In the evaluable population, total deaths was numerically higher in the Infasurf group than in Survanta group (Infasurf 14%, Survanta 8%, p=0.07), and respiratory deaths was statistically significantly higher in the Infasurf group than in the Survanta group (9% vs 4%, p=0.03). In the evaluable TBW Population, (which includes infants from 600 to 1250 grams of birth weight only), total and respiratory mortality were similar (12/158 [8%] vs 11/172 [6%], p=0.67; and 9/158 [6%] vs 5/172 [3%], p=0.21, in Infasurf and Survanta respectively). TABLE 6 shows the cause of death (respiratory or non-respiratory) in the Prophylaxis arm.

TABLE 6. Mortality by cause in the Prophylaxis arm. Number (Percentage) of patients.

PARAMETER	ITT POPULATION			EVALUABLE POPULATION			EVALUABLE TBW POPULATION		
	Infasurf (N=224)	Survanta (N=233)	p-value	Infasurf (N=180)	Survanta (N=194)	p-value	Infasurf (N=158)	Survanta (N=172)	p-value
Total Deaths	40 (18)	25 (11)	0.03	26 (14)	16 (8)	0.07	12 (8)	11 (6)	0.67
Resp. Deaths	4 (11)	9 (4)	0.005	17 (9)	7 (4)	0.03	9 (6)	5 (3)	0.21
Non Respiratory Deaths	16 (7)	16 (7)	0.91	9 (5)	9 (5)	1.00	3 (2)	6 (3)	0.38

In the Treatment arm, there were no statistically significant differences in total deaths, respiratory deaths, or non-respiratory deaths, between Infasurf and Survanta in the ITT and evaluable patients. TABLE 7 shows mortality by cause in the ITT, the evaluable and the evaluable TBW populations.

TABLE 7. Mortality by cause in the Treatment Arm. Number (Percentage) of patients.

PARAMETER	ITT POPULATION			EVALUABLE POPULATION			EVALUABLE TBW POPULATION		
	Infasurf (N=329)	Survanta (N=333)	p-value	Infasurf (N=303)	Survanta (N=305)	p-value	Infasurf (N=251)	Survanta (N=260)	p-value
Total Deaths	63(19)	58(17)	0.62	55(18)	53(17)	0.83	39(16)	44(17)	0.72
Resp. Deaths	44(13)	42(13)	0.79	39(13)	40(13)	1.00	26(10)	33(13)	0.41
Non Respiratory Deaths	19(6)	16(5)	0.59	16(5)	13(4)	0.57	13(5)	11(4)	0.61

Reviewer's note: The difference seen in the incidence of mortality between the surfactant groups, in the prophylaxis trial, was claimed to be due to an unexpectedly low mortality in the infants with birth weight <600 grams in the Survanta group (survival of 74%). A panel of 5 neonatologists, gathered by the sponsor to analyze this issue, was not able to explain the increased survival found in patients weighing less than 600 grams at birth on the Survanta population (not seen in other studies with similar population). This subset consisted of 30 patients in the Infasurf and 23 patients in the Survanta group. TABLE 8 shows the cause of death in patients <600 grams, as presented by the sponsor. The sponsor claims that in the Survanta group of infants of <600 grams less infants died of non-respiratory and late respiratory causes than in the Infasurf group. Those causes were said to be less likely to be influenced by surfactant activity. However, the differences claimed by the sponsor did not reach statistical significance. In addition, when comparing the percentage of cases of respiratory deaths in the ≥ 600 grams between both treatment groups, we find that the Infasurf-treatment group had more than twice the number of deaths observed in the Survanta group. The same is true when comparing the percentage of infants who were < 600 grams dying of respiratory causes. Survanta patients had less respiratory and non-respiratory deaths, as well as total deaths. However, in a post hoc analysis, when total mortality in the ITT population was analyzed excluding those infants <600 grams at birth (TABLE 9), the results in both treatment groups were comparable (p=0.61; 95% CI = -7.6, 4.1).

It is possible that the <600 grams subset was skewed for unknown reasons, unrelated to surfactant therapy, and it drove the whole data to yield a statistically significant difference in mortality in favor of Survanta, difference which could be not a true one. On the other hand, by eliminating the subjects <600 grams, the analysis of the ITT population may have lost the power to demonstrate a true, statistically significant difference. Nevertheless, we should emphasize that the most important analysis in this review is the "all patients ITT" analysis.

TABLE 8. Mortality by cause. ITT, Prophylaxis population <600 grams. Number (percentage) of patients.

	INFASURF (N=30)	SURVANTA (N=23)	p-value*
Early respiratory death, ≤4 days old	4 (13%)	2 (9%)	.69
Late respiratory deaths, >4 days old	5 (17%)	1 (4%)	.22
Non-respiratory deaths	10 (33%)	3 (13%)	.11
Total deaths <600 grams	19 (63%)	6 (26%)	.012

*Fisher's two-tailed test

TABLE 9. Mortality by cause. ITT, Prophylaxis population≥600 grams. Number (percentage) of patients.

	INFASURF (N=194)	SURVANTA (N=210)	P-Value*
Respiratory deaths	13 (8%)	6 (3%)	.10
Non-respiratory deaths	8 (4%)	13 (6%)	.38
Total deaths ≥600 grams	21 (11%)	19 (9%)	.62

*Fisher's two-tailed test

(3) **Chronic Lung Disease**

The definition of chronic lung disease was an oxygen requirement of ≥30% at 28 days of age or any supplemental oxygen dependence at 36 weeks post conceptional age, or 4 weeks of age, whichever was latest.

The patients recruited into the treatment study whose gestational age was 32 weeks of age or more were evaluated for chronic lung disease at 4 weeks of age under both definitions.

There were no statistically significant differences in the incidence of chronic lung disease at 28 days and at 36 weeks PCA in the ITT and the evaluable population, in the Prophylaxis arm. In the treatment trial there was a statistically significant difference in favor of Infasurf at 28 days but not at 36 weeks PCA.

TABLES 10 and 11 show the distribution of patients with chronic lung disease at 28 days and 36 weeks PCA in the prophylaxis and the treatment arms respectively.

TABLE 10. Chronic Lung Disease. Prophylaxis Arm.

VARIABLE	TREATED POPULATION Infasurf (N=224)	Survanta (N=233)	p-value	EVALUABLE POPULATION Infasurf (N=180)	Survanta (N=194)	p-value
Chronic Lung Disease:						
On any 0_2 at 28 days	107(48)	128(55)	0.16	85(47)	111(57)	0.06
On > 30% 0_2 at 28 days	84(38)	80(34)	0.50	67(37)	70(36)	0.83
On ventilator at 28 days	83(37)	96(41)	0.39	66(36)	84(43)	0.21
BPD at 28 days*	84/216 (39)	89/214 (42)	0.62	64/172 (37)	78/175 (45)	0.19
On 0_2 at 36 wks PCA	49/189 (26)	60/217 (28)	0.74	36/156 (23)	50/184 (27)	0.45
Home on oxygen	20/206 (10)	28/223 (13)	0.36	19/166 (11)	24/185 (13)	0.75

* BPD is positive X-ray after day 27 and on O2 at day 28.
Cross Reference: Data Listings 5, 6 in Appendix

TABLE 11. Chronic Lung Disease. Number (percentage) patients. Treatment Arm

VARIABLE	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value
Chronic Lung Disease						
On any 0_2 at 28 days	118(36)	130(39)	0.42	109(36)	117(38)	0.61
On > 30% 0_2 at 28 days	59(18)	82(25)	0.04	54(18)	74(24)	0.06
On ventilator at 28 days	49(15)	62(19)	0.21	46(15)	54(18)	0.44
BPD at 28 days*	76/315 (24)	81/310 (26)	0.58	72/291 (25)	73/285 (26)	0.85
On 0_2 at 36 wks PCA	65/271 (24)	79/278 (28)	0.25	60/252 (24)	74/255 (29)	0.19
Home on oxygen	36/289 (12)	35/291 (12)	0.90	30/268 (11)	33/266 (12)	0.69

* BPD is positive X-ray after day 27 and on O2 at day 28.
Cross Reference: Data Listings 18 and 19 in Appendix

(4) Incidence of RDS - (CNS-P Arm Only) and Severity of RDS (Both Arms).

A. Incidence of RDS

For CNS-P patients, RDS was defined as requiring ≥40 % oxygen at the time for a repeat dose. A diagnosis of RDS was a condition for randomization into the CNS-T study and therefore was not an outcome variable.

B. Severity of RDS

The severity of RDS was assessed by comparing categorical severity of RDS, surfactant retreatment, quantitative respiratory care variables, and the surfactant failure of the two surfactant groups in both arms.

- **Severity of RDS - Categorical:**
  The respiratory care status was abstracted from the medical record at 24 hours of age.

Severe RDS:	**Death or FIO2 ≥70% and MAP ≥12 cm H2O at 24 hours of age.**
Moderate RDS:	**No severe RDS, FIO2 ≥40% and MAP ≥8 cm H2O at 24 hours of age.**
Mild RDS:	**No moderate RDS, FIO2 ≥30% at 24 hours of age.**

- **Surfactant retreatment. Number of doses and dosing interval.**
  The retreatment criteria for surfactant was determined by the continuing or recurring oxygen requirement of the patients for ≥30% inspired oxygen to maintain a PaO_2 of >80 mm Hg or an a/A PO_2 <0.33, measured 6 hours or more after the previous surfactant treatment.

- **Quantitative Respiratory Care Variables**
  Inspired oxygen (FIO2) and mean air pressure (MAP) were compared at different time points up to 72 hours of age to provide quantitative comparisons at different stages of RDS. Ventilator and oxygen data were abstracted from the medical record.

- **Surfactant Failure**
  This is an outcome which grouped all patients in each treatment arm who received cross over, received more than 4 doses of the randomized surfactant or their physicians decided the patient urgently required surfactant therapy inconsistent with the study protocol.

(1) Prophylaxis Arm:

(a) Incidence of RDS . There were no statistically significant differences between both treatments in the ITT and the evaluable population;

(b) Severity of RDS. There were no statistically significant differences between the treatment groups with respect to total doses required, categorical severity of RDS at 24 hours, surfactant failure and respiratory support for the first 72 hours in the ITT and the evaluable population. The interval between doses 2, 3 and 4 was statistically significantly shorter for the Survanta than the Infasurf patients in the ITT and the evaluable population.

TABLE 12 shows the incidence of RDS and the severity of RDS analyzed by its different elements in the ITT and the evaluable population of the prophylaxis arm.

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TABLE 12. Incidence and severity of RDS. ITT and Evaluable population. Prophylaxis arm.

Outcomes of RDS Severity	TREATED POPULATION Infasurf (N=224)	Survanta (N=233)	p-value	EVALUABLE POPULATION Infasurf (N=180)	Survanta (N=194)	p-value
Incidence of RDS	108(48)	106(45)	0.55	77(43)	84(43)	1.00
Number of Surfactant Doses						
Only one dose	104(46)	113(48)		93(52)	99(51)	
Only two doses	33(15)	32(14)		28(15)	26(13)	
Only three doses	34(15)	27(11)		24(13)	19(10)	
Four + doses	53(24)	61(27)	0.81*	35(19)	50(26)	0.30*
Hours dose 1 to dose 2	15±12	13±14	0.27	15±12	12±12	0.10
Hours dose 2 to dose 3	18±17	11±8	0.0006	18±19	11±8	0.005
Hours dose 3 to dose 4	16±14	11±8	0.02	17±16	11±8	0.04
Respiratory Support:						
FIO2						
at 6 hours	37±21	38±19	0.58	37±21	38±20	0.41
at 12 hours	32±18	34±18	0.17	31±18	34±17	0.18
at 18 hours	31±15	31±13	0.86	31±15	31±13	0.95
at 24 hours	30±13	31±12	0.42	30±11	0.55	
at 48 hours	30±15	30±13	0.88	28±13	30±13	0.31
at 72 hours	27±9	28±13	0.16	26±9	27±11	0.29
MAP						
at 6 hours	7.6±2.5	7.6±2.1	0.76	7.6±2.6	7.6±2.0	0.89
at 12 hours	6.6±2.7	6.6±2.4	0.84	6.5±2.5	6.6±2.3	0.59
at 18 hours	5.9±2.6	5.8±2.4	0.90	5.8±2.6	5.8±2.4	0.95
at 24 hours	5.3±2.6	5.4±2.6	0.72	5.2±2.7	5.3±2.6	0.89
at 48 hours	5.1±3.2	5.0±3.0	0.71	4.9±3.2	5.0±3.0	0.91
at 72 hours	4.8±3.2	4.5±3.1	0.40	4.6±3.3	4.4±3.1	0.58
RDS Severity at 24 hours						
Severe	11(5)	3(1)		10(6)	3(2)	
Moderate	9(4)	17(7)		6(3)	12(6)	
Mild	65(29)	72(31)		51(28)	57(29)	
None	139(62)	141(61)	0.07*	113(63)	122(63)	0.12*
Surfactant Failure	13(6)	17(7)	0.57	10(6)	15(8)	0.42

* Distribution P value

Cross Reference: Data Listings 7, 8, and 9 in Appendix.

Reviewer's note: The protocol definition of RDS entailed only a requirement of FiO2 ≥40% at the time of the repeat dose. No correlation with blood oxygen or CXR status was required, this fact could potentially have led caregivers to subjective management of the patients based on diverse criteria for diagnosis and assignment of severity of RDS. Thus, the result of the data is difficult to interpret. Overall, there were no statistically significant differences in incidence of RDS or in the length of activity of both surfactants.

(2) **Treatment Arm:**

Severity of RDS: There was a statistically significant difference in favor of Infasurf in number of doses and dose intervals, severe pattern of RDS at 24 hours of age, oxygen requirements and mean airway pressures (MAP) at 24 hours. At 48 and 72 hours of age, differences in oxygen need and mean airway pressures were no longer statistically significantly different. Surfactant failure was infrequent in both groups and similar in incidence. TABLE 13 shows the severity of RDS analyzed by its different elements in the ITT and the evaluable population of the treatment arm.

TABLE 13. Severity of RDS. ITT and Evaluable population. Treatment arm.

Outcomes of RDS Severity	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value
Number of Surfactant Doses received						
One dose	94(29)	109(33)		90(30)	103(34)	
Two doses	88(27)	72(22)		82(27)	64(21)	
Three doses	67(20)	39(12)		64(21)	37(12)	
Four or more doses	80(24)	113(34)	0.002*	67(22)	101(33)	0.002*
Hours dose 1 to dose 2	13±11	10±9	<0.001	13±11	10±9	0.00014
Hours dose 2 to dose 3	13±11	9±5	<0.001	13±10	9±5	0.0001
Hours dose 3 to dose 4	12±11	8±5	0.006	12±12	8±5	0.005
Respiratory Support: FIO2						
at 6 hours	57±26	60±25	0.02	55±25	60±25	0.02
at 12 hours	43±24	47±24	0.07	43±23	47±24	0.04
at 18 hours	37±19	41±21	0.02	36±18	41±21	0.01
at 24 hours	35±18	40±21	0.002	34±16	39±21	0.0005
at 48 hours	36±19	37±21	0.60	35±18	36±20	0.62
at 72 hours	35±19	33±17	0.31	34±18	33±17	0.58
MAP						
at 6 hours	7.9±3.4	8.5±3.3	0.02	7.8±3.3	8.5±3.3	0.006
at 12 hours	7.3±3.0	7.9±3.4	0.02	7.2±3.0	7.9±3.4	0.01
at 18 hours	6.3±2.7	6.9±2.5	0.005	6.2±2.7	6.8±2.5	0.005
at 24 hours	5.7±2.9	6.3±2.7	0.01	5.7±2.9	6.2±2.7	0.01
at 48 hours	5.1±3.6	5.1±3.6	0.79	5.0±3.6	5.1±3.6	0.89
at 72 hours	4.6±4.1	4.4±3.7	0.43	4.6±4.1	4.4±3.8	0.53
RDS Severity at 24 hours						
Severe	17(5)	22(7)		13(4)	21(7)	
Moderate	23(7)	46(14)		19(6)	39(13)	
Mild	121(37)	133(40)		114(38)	123(40)	
None	168(51)	132(40)	0.004*	157(52)	122(40)	0.004*
Surfactant Failure	25(8)	29(9)	0.67	22(7)	24(8)	0.88

* Distributional P value

Cross Reference: Data Listings 20, 21, and 22 in Appendix.

Reviewer's note: Even though this trial showed a statistically significant difference in variables of respiratory support in favor of Infasurf (number of doses required, length of interval between doses, respiratory support at 24 hours, and categorical RDS at 24 hours), there is no indication of a clinically significant difference between the two treatment groups, for instance, a difference of 0.6 in MAP. The aim of the study to show a reduction of at least 25% in the fraction of Infasurf patients that would require 3 or more doses as an indicator of increased activity was not met. In fact, the percent of patients that required 3 or more doses of surfactant was almost identical in both treatment groups, i.e., 45% for Infasurf and 46% for Survanta patients.

(5) Pulmonary Complications of RDS

Pneumothorax, parenchymal interstitial emphysema (PIE), total air leaks and pulmonary hemorrhages were considered pulmonary complications of RDS.

There was no statistically significant difference between both treatment groups when compared by pulmonary complications of RDS (TABLE 14 shows the pulmonary complications in the ITT and evaluable population of the Prophylaxis arm, TABLE 15 displays the same data in the Treatment arm).

TABLE 14. Pulmonary complications of RDS. Prophylaxis arm. Number (percentage) of patients.

Complications of RDS	TREATED POPULATION			EVALUABLE POPULATION		
	Infasurf (N=224)	Survanta (N=233)	p-value	Infasurf (N=180)	Survanta (N=194)	p-value
Pneumothorax	21(9)	14(6)	0.22	16(9)	9(5)	0.15
PIE	23(10)	13(6)	0.08	14(8)	11(6)	0.54
Pneumomediastinum	3(1)	1(<1)	0.36	3(2)	1(1)	0.36
Any Air Leak	34(15)	24(10)	0.12	23(13)	19(10)	0.41
Pulmonary Hemorrhage	16(7)	14(6)	0.71	11(6)	12(6)	1.00

Cross Reference: Data Listing 10 in Appendix

TABLE 15. Pulmonary complications of RDS. Treatment arm. Number (percentage) of patients.

Complications of RDS	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value
Pneumothorax	22(7)	34(10)	0.12	18(6)	31(10)	0.07
PIE	33(10)	44(13)	0.23	29(10)	42(14)	0.13
Pneumomediastinum	5(2)	8(2)	0.58	4(1)	6(2)	0.75
Any Air Leak	51(16)	59(18)	0.47	44(15)	55(18)	0.27
Pulmonary Hemorrhage	21(6)	22(7)	1.00	18(6)	18(6)	1.00

Cross Reference: Data Listing 23 in Appendix

C. Safety Outcomes

(1) Serious Complications of Prematurity

The following complications of prematurity were monitored:

- patent ductus arteriosus (PDA),
- intraventricular hemorrhage (IVH),
- periventricular leukomalacia (PVL),
- necrotizing enterocolitis (NEC),
- retinopathy of prematurity (ROP) and
- sepsis.

No significant differences were found in the incidence of complications of prematurity in either arm. TABLES 16 and 17 show serious complications of prematurity in the prophylaxis and the treatment arm respectively.

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TABLE 16. Serious Complications of Prematurity: Prophylaxis Arm

COMPLICATIONS	TREATED POPULATION Infasurf (N=224)	Survanta (N=233)	p-value	EVALUABLE POPULATION Infasurf (N=180)	Survanta (N=194)	p-value
Seizures	11(5)	9(4)	0.65	7(4)	5(3)	0.56
Number with Neuroimaging	218	227		175	193	
IVH only [a]	81(37)	71(31)	0.17	67(38)	58(30)	0.11
PVL only	5(2)	3(1)	0.50	3(2)	3(2)	1.00
IVH and PVL	11(5)	13(6)	0.84	8(5)	11(6)	0.65
IVH and/or PVL	97(44)	87(38)	0.15	78(45)	72(37)	0.16
Mild IVH only[b]	78(36)	73(32)	0.43	65(37)	59(31)	0.13
Severe IVH[c]	14(6)	11(5)	0.52	10(6)	10(5)	0.82
Died, or survived with PVL and/or severe IVH[d]	52(23)	39(17)	0.10	35(19)	32(16)	0.50
Survived without either PVL or severe IVH	172(77)	194(84)	0.10	145(81)	162(84)	0.50
PDA*	122/155 (79)	130/165 (79)	1.00	94/120 (78)	107/138 (78)	1.00
Other complications[d]						
NEC	56(25)	52(22)	0.51	46(26)	46(24)	0.72
Apnea	193(86)	203(87)	0.79	156(87)	173(89)	0.53
ROP	57(25)	71(30)	0.25	48(27)	62(32)	0.31
RLF	1(<1)	1(<1)	1.00	1(1)	1(1)	1.00
Sepsis	77(34)	78(33)	0.92	60(33)	63(32)	0.91

[a] Percentages of IVH and PVL calculated on number with neuroimaging
[b] Mild IVH is Grades I and II by Papile method of grading.
[c] Severe IVH is Grades III and IV by Papile method of grading.
[d] Percentages for these complications calculated on total number.
* Patent Ductus Arteriosus required ultrasound verification, denominator is number evaluated.
Cross Reference: Data Listings 12, 13 in Appendix

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TABLE 17. Serious Complications of Prematurity: Treatment Arm

COMPLICATIONS	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value
CNS complications						
Seizures	22(7)	34(10)	0.13	19(6)	31(10)	0.10
Number with Neuroimaging	295	295		275	268	
IVH only [a]	102(35)	116(39)	0.14	98(36)	104(39)	0.33
PVL only	2(1)	2(1)	1.00	2(1)	2(1)	1.00
IVH and PVL	16(5)	17(6)	1.00	15(5)	17(6)	0.72
IVH and/or PVL	120(41)	135(46)	0.13	115(42)	123(46)	0.24
Mild IVH only[b]	84(28)	104(35)	<0.001	82(30)	94(35)	0.20
Severe IVH[c]	34(12)	29(9)	0.41	31(11)	27(10)	0.68
Died, or survived with PVL and/or severe IVH[d]	75(23)	68(20)	0.51	69(23)	62(20)	0.49
Survived without either PVL or severe IVH	254(77)	265(80)	0.51	234(77)	243(80)	0.49
PDA*	125/183 (68)	143/182 (79)	0.03	114/168 (68)	118/157 (75)	0.18
Other complications[d]						
NEC	36(11)	52(16)	0.09	33(11)	46(15)	0.15
Apnea	229(70)	227(68)	0.68	217(71)	206(68)	0.25
ROP	53(10)	51(35)	0.83	51(17)	43(14)	0.37
Sepsis	78(24)	77(23)	0.85	69(23)	73(24)	0.85

[a] Percentages of IVH and PVL calculated on number with neuroimaging
[b] Mild IVH is Grades I and II by Papile method of grading.
[c] Severe IVH is Grades III and IV by Papile method of grading.
[d] Percentages for these complications calculated on total number.
* Patent Ductus Arteriosus required ultrasound verification, denominator is number evaluated.
Cross Reference: Data Listings 25, 26 in Appendix

Reviewer's note: For both arms Infasurf patients presented PVL's alone or combined with IVH comparable to Survanta. Infasurf did have a small numerical increase in the incidence of severe IVH without reaching statistical significance. In this trial Infasurf did not have such an increase in intracranial bleeding above its active control as it did in the Infasurf-Exosurf trials. However, the post-hoc analysis, comparing the number of patients who died plus those who had PVL or severe IVH between both treatment groups, showed that Infasurf could be as much as 14% worse than Survanta in this endpoint.

95% CI's - Patients who died, or survived with PVL and/or severe IVH

ITT	Infasurf	Survanta	P-value	95% CI Inf-Exo
Prophylaxis	N=224	N=233		
Endpoint	52(23%)	39 (17%)	0.10	(-0.8, 13.8)
Treatment	N=329	N=333		
Endpoint	75 (23%)	68 (20%)	0.51	(-3.9, 8.6)

(2) — Adverse Events at Administration

In both arms the following complications were recorded:

- **Bradycardia (heart rate <100/minute)**
- **Airway obstruction**
- **Extubation**
- **Change in systolic blood pressure (SBP) (>5 mmHg)**
- **Required suctioning within 1 hour**

In the ITT population of the prophylaxis arm, Infasurf patients had statistically significantly more suctioning within 1 hour (p=0.03), and had numerically more airway obstruction (p=0.08), than Survanta patients. In the evaluable population there were no statistically significant differences between both treatment groups. However, there was a trend toward more patients in the Infasurf group requiring suctioning within 1 hour of the administration of the surfactant. TABLE 18 shows the incidence of adverse events in the ITT and evaluable population of the prophylaxis arm.

TABLE 18. Adverse events . Prophylaxis arm. Number (percentage) of patients.

Adverse events At Any Dose, 1- 5	TREATED POPULATION Infasurf (N=224)	Survanta (N=233)	p-value	EVALUABLE POPULATION Infasurf (N=180)	Survanta (N=194)	p-value
Bradycardia	31(14)	37(16)	0.60	26(14)	27(14)	0.88
Airway obstruction	9(4)	3(1)	0.08	8(4)	3(2)	0.13
Extubated	5(2)	5(2)	1.00	4(2)	4(2)	1.00
ΔSBP > 5 mmHg	3(1)	1(<1)	0.36	3(2)	1(1)	0.36
Suctioned within 1hr	16(7)	6(3)	0.03	11(6)	4(2)	0.06
Any adverse event	41(18)	46(20)	0.72	32(18)	34(18)	1.00

Cross Reference: Data Listing 1 1 in Appendix

In the treatment arm, statistically significantly more patients in the Infasurf group had airway obstruction (p=0.04) and numerically more patients required suctioning within 1 hour after the administration of surfactant than in the Survanta group. TABLE 19 shows the incidence of adverse events during the administration of surfactant in the ITT and evaluable population of the treatment arm.

TABLE 19. Adverse events . Treatment arm. Number (percentage) of patients.

Adverse events At Any Dose, 1-5	TREATED POPULATION Infasurf (N=329)	Survanta (N=333)	p-value	EVALUABLE POPULATION Infasurf (N=303)	Survanta (N=305)	p-value
Bradycardia	52(16)	50(15)	0.83	49(16)	43(14)	0.50
Airway obstruction	9(3)	2(1)	0.04	7(2)	2(1)	0.11
Extubated	3(1)	0(0)	0.12	3(1)	0(0)	0.12
ΔSBP > 5 mmHg	54(16)	54(16)	1.00	48(16)	43(14)	0.57
Suctioned within 1hr	21(6)	11(3)	0.07	19(6)	9(3)	0.06
Any adverse event	97(29)	94(28)	0.73	89(29)	79(26)	0.37

Cross Reference: Data Listing 24 in Appendix

Reviewer's note: The adverse events reported during the administration of Infasurf in both trials demonstrate an overall increase in airway obstruction and the consequent need of suctioning within 1 hour of its administration. However, adverse events, during the administration of Infasurf in these trials, were of a lesser magnitude (no increase in the incidence of bradycardia or hypotension) than that seen for Infasurf in the SCT trials, where Infasurf had a marked incidence of bradycardia, cyanosis, airway obstruction and reintubations. In those trials Infasurf was administered directly in the ETT following Exosurf instructions of administration. In the present trial, Infasurf was administered following Survanta instructions.

12. Summary

PROPHYLAXIS TRIAL

In the prophylaxis trial, a total of 224 patients received Infasurf and 233 patients received Survanta. Their demographic and obstetric characteristics were basically similar. The maximum number of doses administered to any one patient was 5. Seventy six percent of the patients in the Infasurf group, and 73% in the Survanta group received a total of 3 doses or less .

<u>Results That Support Comparability of Infasurf to Survanta</u>

Infasurf was comparable to Survanta in terms of intact cardiopulmonary

survival to day 28 and to 36 weeks PCA, chronic lung disease defined as requirement of ≥30% oxygen at day 28, severity of RDS in its different measuring variables, complications of RDS, and complications of prematurity.

Infasurf treatment had similar results to Survanta in the incidence of RDS, endpoint in which Survanta consistently showed superiority over placebo.

Results That Indicate Infasurf Was less Effective than Survanta
The Infasurf-treated group had a statistically significant increase in total deaths and in respiratory deaths (p=0.03 and 0.005 respectively). The 95% CI for the difference in total deaths between Infasurf and Survanta was -13.5, and -0.73, indicating that Infasurf might be as much as 13.5% worse than Survanta.

Infasurf had a significant increase in the need for suctioning within the first hour after the instillation of the surfactant. This variable can be paired with airway obstruction, which had a numerical increase without statistical significance (p=0.08) in the Infasurf group over the Survanta group.

TREATMENT TRIAL
In the treatment trial, 329 patients received at least one dose of Infasurf and 333 patients received Survanta. The demographic and obstetric variables were comparable between both groups. The maximum number of doses administered to any one patient was 5. Seventy eight percent of the patients in the Infasurf group, and 67% in the Survanta group received a total of 3 doses or less .

Results That Support Superiority of Infasurf to Survanta
In this trial Infasurf showed a statistically significant decrease in the severity of RDS, measured by predefined variables, i.e., longer between-dose intervals, less FiO2 supplement and less MAP required up to 24 hours. The difference in these parameters between both treatment groups was no longer significant at 48 and 72 hours post treatment, and the clinical significance of the magnitude of the differences in FiO2 and MAP is questionable.

Infasurf had statistically significantly less incidence of chronic lung disease at 28 days defined as the need of FiO2 ≥30% at 28 days (it was not statistically significant at 36 weeks).

Results That Support Comparability

The two surfactants were comparable in total mortality, endpoint that Survanta showed to be superior to placebo in one of its pivotal studies (p= 0.001), and numerically better without statistical significance (p = 0.285) in another. Infasurf also had similar results to Survanta in respiratory mortality; intact CP survival; chronic lung disease at 36 weeks PCA; incidence of BPD, defined as the need of any O2 and a positive CXR at 28 days; complications of RDS and complications of prematurity.

Results That Indicate Infasurf Was less Effective than Survanta

As in the Infasurf-Exosurf trials, Infasurf presented a statistically significant increase in adverse events during its administration compared to Survanta. More patients presented airway obstruction (p=0.04) and numerically more patients needed suctioning within the first hour after the administration of Infasurf (p=0.07).

13. Discussion and Conclusions

The prophylaxis arm, of the clinical trial comparing Infasurf to Survanta, Infasurf failed to demonstrate efficacy , as indicated by the increase in total mortality and mortality due to respiratory causes in the Infasurf treated population. However, Infasurf did show comparable results to Survanta in the prevention of RDS. In the treatment arm, Infasurf demonstrated similar results in the efficacy endpoints to that of Survanta. Both arms showed a tendency in the right direction to decrease the incidence of chronic lung disease at 28 days and 36 weeks PCA. In regard to safety, Infasurf presented again a statistically significant increase in the incidence of adverse events (airway obstruction /suctioning) during its administration. Even when these adverse events were considered transient and moderate in nature, they imposed some increased risks to these already fragile population, and their occurrence should be discussed properly in the label.

IV. UNCONTROLLED STUDIES

1. **Protocol 8901 / "Rescue treatment of Hyaline Membrane Disease with Infasurf (Calf Lung Surfactant extract). Ref. vol 1.32 .**

   A. **Study Characteristics and Definitions.**
   This was a multicenter (14 centers), open-label, randomized trial of infants of 28 to 38 weeks gestational age, with random allocation to either early treatment with Infasurf or control. Neonates in the treatment group received Infasurf for the treatment of moderate or severe RDS while the neonates randomized to the control group did not receive treatment with Infasurf unless they developed severe RDS. All patients received the same dose of Infasurf (3 ml/Kg , 35 mg/ml); both groups were retreated if they met the criteria for severe RDS more than once. There were no criteria on frequency and total of doses to be given.

   Severe RDS was defined initially as requiring inspired oxygen ≥70% and a mean airway pressure (MAP)≥12 cmH2O (The data that used this definition was reported as for Period I). Six months later the definition was changed to FiO2 ≥60% and of MAP ≥10 cm H2O (Period II).

   Moderate RDS during Period I was defined as requiring FiO2 40-69% to maintained PaO2 >60 torr, MAP 8-11.9 cmH2O to maintain PaCO2<50 torr, with CXR findings characteristic of RDS. During Period II it was changed to RDS that requires FiO2 40-59% and MAP 5- 9.9 cmH2O.

   B. **Objectives.**
   The study objectives were to determine if Infasurf was effective in limiting the progression of moderate RDS and to determine if altering the progression of RDS would decrease the incidence of mortality and the severity of complications of prematurity and RDS.

   C. **Results.**
   There were no statistically significant differences in the demographic characteristics of both groups. Sixty of 256 infants (23%) in the treatment group developed severe RDS compared to 133 of 243 infants (55%) in the control group ($p \leq 0.01$) in a combined analysis (Periods I and II). Each period separately was also significantly better for the Infasurf treated than the control group. There was no statistically significant difference between the two groups in the incidence of lung air leaks, chronic lung disease or death for either period.

D. Comments.

Four hundred and ninety-nine infants were randomized in this trial, 256 were randomized to the treatment group and 243 to control. Of the 499 infants, 481 were administered Infasurf as either a prophylactic therapy, a rescue therapy, or both, as part of another study (study 8701). Only 18 patients (probably of the control group) were never exposed to Infasurf at some point. Though the report does not state how many patients received Infasurf prior to randomization, it does say that some patients had received Infasurf prior to enrollment. The results of this trial are difficult if not impossible to elucidate especially from the safety point of view, since patients within both groups were exposed to the test drug before onset of the study at an unknown degree; further more, most of the control group received it as a rescue therapy during the trial. In addition, there were no criteria as the number of retreatments or the frequency of them. The open label nature of the trial is a flaw, particularly when the endpoint is a soft variable as opposed to a "harder", more objective parameter e.g., incidence of death.

2. Study 8902/ Comparison of Early "Rescue" and Prophylaxis at Birth. Ref. Vol. 1.33.

A. Study Characteristics and Definitions.

This was a multicenter (9 centers), open label trial with randomization to either prophylaxis or rescue treatment with Infasurf. A total of 1398 infants, between 29 and 32 weeks of gestational age were enrolled. Six hundred twenty-seven infants were included in the prophylaxis group and 621 infants were treated in the rescue population (79 patients in the prophylaxis and 71 patients in the rescue groups were discontinued from the study due to deviations from the protocol). Patients could receive up to 3 doses of Infasurf (4.5 ml, 150 mg). Patients in the rescue group were eligible for treatment if they developed mild respiratory distress, findings of RDS in CXR and FiO2 >30%. Each analysis included all rescue treatment patients, even those who were eligible for rescue but never required Infasurf. Patients in the prophylaxis group were intubated immediately post delivery and the first dose of Infasurf was administered.

The primary efficacy variables were the incidence of moderate and severe RDS. Secondary measures of efficacy were incidence of death and duration of respiratory support for the first 96 hours of life.

Mild RDS was defined as CXR with reticulo-granular infiltrates with or without an air bronchogram and a FiO2 reading ≥ 30%.

Moderate RDS was defined as requiring a FiO2 >40% with a MAP > 8 cmH2O.

Severe RDS was defined as requiring a FiO2 > 60% and a MAP >10 cmH2O. CXR findings and a defined arterial PO2 were not applicable to the definition. Retreatment was allowed at 8 hour intervals.

B. Objectives.

The objective of this trial was to determine if the administration of Infasurf immediately following birth was preferable to delaying administration until after the development of RDS.

C. Results.

Demographic Characteristics

There were no clinically or statistically significant differences between the treatment and the prophylaxis groups with respect to birth weight, race, sex, congenital anomalies and APGAR score at 5 minutes. The prophylaxis group had a statistically significant lower 1 minute APGAR score (5.7 vs. 6.3, p-value 0.0001) than the rescue group.

Efficacy

In the rescue group, 43% of patients developed mild RDS and consequently received Infasurf. The median age at treatment was 1.5 hours and 70% of the rescue patients received their first dose by 3 hours of age. See TABLE 1 for the distribution of patients who received Infasurf by gestational age and birth weight per arm. All patients randomized to the prophylaxis arm received Infasurf. Patients who were randomized to the treatment arm, received Infasurf only if they met RDS criteria. This table shows that patients <30 weeks gestation and <1500 g of birth weight received Infasurf > 50% of the time. Above this limit, the use of Infasurf decreased markedly.

Significantly more patients in the rescue population developed moderate and severe RDS than in the prophylaxis population (p-values <0.001 and 0.023 respectively). In the rescue group more patients died and less survived to day 28 without requiring oxygen supplement than in the prophylaxis group. TABLE 2 shows the efficacy variables by treatment group.

TABLE 1. Patients who received Infasurf. (percentage) of evaluated patients.

	Prophylaxis Population* [N=627]	Rescue Population* [N=621]
Gestational Age (weeks)		
29	99/99 (100)	64/101 (63)
30	123/123 (100)	70/134 (52)
31	158/158 (100)	58/161 (36)
32	247/247 (100)	72/225 (32)
All	627/627 (100)	264/621 (43)
Birth Weight (grams)		
≤ 1250	99/99 (100)	44/83 (53)
1251-1500	154/154 (100)	82/157 (52)
1501-1750	165/165 (100)	78/185 (42)
> 1750	209/209 (100)	60/196 (31)
All	627/627 (100)	264/621 (43)

* of patients treated with Infasurf / total of patients in subgroup (percentage).
Cross Reference: Data Listing 1 of Case Report Tabulations (NDA Section XI)

TABLE 2. Efficacy variables per treatment group. (percentage) of patients.

PARAMETER	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
Moderate RDS	39 (6)	79 (13)	< 0.0001
Severe RDS	5 (1)	15 (2)	0.023
PIE	3 (<1)	3 (<1)	0.991
Pneumothorax	8 (1)	11 (2)	0.475
Any air leak	10 (2)	12 (2)	0.651
Total deaths	3 (<1)	11 (2)	0.030
Survival with no O2 at 28 days	599/627 (96)	568/621 (92)	0.003
BPD	29/624 (5)	44/612(7)	0.07
Total Deaths	3 (<1)	11 (2)	0.030
Death due to RDS	0 (0)	1 (<1)	0.315
Death at 7 days	2 (<1)	8 (1)	0.055
Death at 28 days	3 (<1)	9 (2)	0.079
Survival to discharge	624 (99.5)	610 (98)	0.033

Cross Reference: Data Listing 3 and 4 of Case Report Tabulations (NDA Section XI)

TABLE 3. Mortality by Gestational Age and Birth Weight - (Percentage) of Evaluated Patients

	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
Gestational Age			
(weeks) ≤ 29	0/99 (0)	5/101 (5)	0.059
30	2/123 (2)	3/134 (2)	NS
31	1/158 (1)	1/161 (1)	NS
≥ 32	0/247 (0)	2/225 (1)	NS
All	3/627 (1)	11/621 (2)	0.033
Birth Weight (grams)			
≤ 1250	0/99 (0)	4/83 (5)	0.042
1251-1500	1/154 (1)	4/157 (3)	NS
1501-1750	2/165 (1)	3/185 (2)	NS
> 1750	0/209 (0)	0/196 (0)	NS
All	3/627 (<1)	11/621 (2)	0.033

Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

Safety

The most frequently reported complication documented among neonates in the prophylaxis population were PDA (21%), IVH (13%) and sepsis (6%). In the rescue population, the most frequently documented events were the same: PDA (26%), IVH (14%) and sepsis (6%).

With the exception of PDA, there were no statistically significant differences in most of the complications commonly found in this set of the population between the prophylaxis and treatment groups. TABLE 4 presents the incidence of the most common complications of prematurity in the prophylaxis and the rescue population.

TABLE 4. Incidence of Complications of Prematurity.

Parameter	Prophylaxis Population [N=627]	Rescue Population [N=621]	p-Value
IVH	79/627 (13)	84/621 (14)	0.627
PVL	15/627 (2)	7/621 (1)	0.159
Pulmonary hemorrhage	0/627 (0)	2/621 (<1)	0.155
Patent ductus arteriosus	130/627 (21)	159/621 (26)	0.041
Necrotizing enterocolitis	30/627 (5)	28/621 (5)	0.817
ROP	23/500 (5)	12/489 (3)	0.188
Retrolental fibroplasia	2/510 (< 1)	1/501 (< 1)	0.574
Shock	12/626 (2)	17/620 (3)	0.334
Seizure	11/627 (2)	5/620 (1)	0.137
Sepsis	38/627 (6)	37/621 (6)	0.939
Home on oxygen	19/627 (3)	28/621 (5)	0.170

Cross Reference: Data Listings 6A and 6B of Case Report Tabulations (NDA Section XI)

D. Comments

Even though this protocol has some flaws mentioned below, it does provide interesting comparisons of outcomes between the prophylaxis and the treatment arms in the different age and birth weight subsets.

The study report does not provide follow up information on patients excluded after randomization: one hundred and fifty patients (79 patients in the prophylaxis and 71 patients in the rescue groups) were withdrawn after randomization because either they did meet exclusion criteria (148 patients), their data was lost (1 patient), or the patient was born outside of the site (1 patient). TABLE 5 presents the causes of withdrawal.

TABLE 5. Causes of withdrawal of patients.

Number of Infants	Prophylaxis Population	Rescue Population
Total number dropped from study	79	71
Reason dropped from study		
Congenital anomalies	32	30
Congenital sepsis/pneumonia	22	23
Judged too mature	22	17
Severe perinatal asphyxia	2	0
Lost data	1	0
Not born at a clinical site	0	1

In addition, the definitions of RDS (mild, moderate or severe) do not include PaO2 or any other oxygenation parameter reflective of the patient's gas exchange status, leaving the diagnosis per se and the assignment of severity of RDS up to the individual investigator's style of patient management. The assignment of BPD included patients with oxygen supplementation at 28 days, and "those that the investigator answered yes, (as with BPD) in the CRF" -it is unknown what was the criteria followed by the investigators for determination of BPD, and what was the proportion of patients who received this assignment. There is no validation of the cause of death assignments - total death was mostly due to causes other than respiratory (there were only 3 patients classified as with a respiratory cause of death, all in the rescue group). Only one case had assigned RDS as a cause of death. These facts, in an open label trial make the results difficult to interpret.

Nevertheless, the value of this trial rests on the comparison of outcomes by birth weight and gestational age between groups where the surfactant was given as prophylaxis and when it was given when the patient already had mild RDS. Its results point out that the risk of developing RDS is greater than 50% at < 30 weeks of gestational age, and at a birth weight of < 1500 g. Prophylactic treatment was statistically significantly lower in mortality of any cause in those patients of <29 weeks gestational age and < 1250 g of birth weight, even though we have to have in mind that the mortality rate in any case was low and that the causes of death were categorized mostly as not related to respiratory causes.

3. Study 9303/ Interim Open-label Trial of Infasurf . Ref. Vol 1.33.

A. Study Characteristics and Definitions.
This was a phase III, multicenter (8 centers), open label, uncontrolled, not randomized trial. One hundred ninety-seven infants were enrolled; 72 infants were treated in the prophylaxis population, 118 were treated in the rescue treatment population and seven infants were treated after failing therapy with another surfactant. Prophylaxis treatment with Infasurf was offered to infants whose calculated gestational age was less than 29 weeks. Infants with documented lung maturity before birth were excluded. Rescue treatment was offered if the infant had RDS, was intubated, had not been treated with another surfactant, and required more than 40% oxygen to maintain PaO_2 > 80 torr or had an arterial:alveolar PO_2 (a/A PO_2) < 0.22. Infants who were initially treated with another surfactant were eligible to enter into the study if they had severe and progressive RDS which was defined as mean airway pressure (MAP) of > 10 cm H_2O and FiO_2 > 60%. All infants received the same dose of Infasurf (3 mL/kg of 35 mg of

phospholipid /mL) regardless of treatment population. Prophylaxis infants received a total of three doses of study drug. The first dose was administered at birth and repeat doses were given 12 and 24 hours later if endotracheal intubation was still in place. Rescue treatment and surfactant failure patients received a total of two doses; the second dose was administered 12 hours after the initial dose if endotracheal intubation was still in place.

The primary efficacy endpoint was the incidence of RDS for the prophylaxis group, and the incidence of RDS-related air leaks for the rescue treatment and surfactant failure groups. Secondary outcomes were severity of RDS and incidence of RDS-related air leaks (for the prophylaxis group only), RDS deaths, total deaths and BPD (for all groups).

B. Objectives.

The primary objective was the collection of additional efficacy and safety data on patients treated with Infasurf for prophylaxis of respiratory distress syndrome (RDS) or treatment of RDS. A secondary objective was to provide a mechanism to allow clinical sites who had participated in the Surfactant Comparison Trial (Protocol 9101) to administer Infasurf to their patients, if they wished, on an interim basis.

C. Results.

(1) Demographic Characteristics

TABLE 1. Demographic Characteristics

PARAMETER	PROPHYLAXIS (N=72)	RESCUE TREATMENT (N=118)	SURFACTANT FAILURE (N=7)
Birth weight (grams)*	916	1658	1517
Gestational age (wks)*	27	31	30
Sex (male)	41 (57)	68 (58)	4 (57)
Race (Caucasian)	50 (69)	96 (81)	6 (86)
Apgar score 1 min.* 5 min.*	 4 7	 6 7	 5 8

* Mean

Cross Reference: Data listing 1 of Case Report tabulations (NDA section XI)

(2) **Efficacy**

For the prophylaxis group, 22% of the patients developed RDS (defined as a CXR positive for RDS at 16 to 32 hours and a requirement of FiO2 ≥ 30% at the time of the CXR, to maintain PaO2> 50 torr). In the Prophylaxis arm of the Study 9101- SCT, the incidence of RDS (its definition was similar to this one) was 16% (Mean birth weight was 896 g) in the Infasurf group and 47% in the Exosurf group (Mean birth weight = 900 grams).

RDS-related air leaks included pneumothoraces and parenchymal interstitial emphysema (PIE). In the rescue treatment and surfactant failure group, there were 22% and 29% incidence of any RDS-related air leak respectively. In Study 9101- SCT, the treated arm of the Infasurf group (mean birth weight =1648 g) had an incidence of RDS-related air leaks of 10.5 to 14% , and the Exosurf group (mean birth weight = 1564 g), had an incidence of 22 to 25%.

TABLE 2. Incidence of Air Leaks in Study Populations - (Percentage) of Patients

Parameter	Prophylaxis Population [N=72]	Rescue Treatment Population [N=118]	Surfactant Failure Population [N=7]
Any Air Leak	17 (24)	26 (22)	2 (29)
PIE	12 (17)	11 (9)	–
Pneumothorax	4 (6)	20 (17)	–

–Not Assessed
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

The secondary outcomes are presented in TABLE 3. Even though the study populations were similar to that of study 9101-SCT, the incidence of RDS death and total mortality in this trial were markedly higher than those registered in the Infasurf group of Study 9101-SCT (For the prophylaxis group RDS death was 2.1% and total death to 28 days was 12%; for the rescue group RDS death was 3.5% and total mortality to day 28 was 8%). The reasons for this increase are not clear.

TABLE 3. Secondary Efficacy Outcomes - (Percentage) of Patients

Parameter	Prophylaxis Population [N=72]	Rescue Treatment Population [N=118]	Surfactant Failure Population [N=7]
Severity of RDS None Mild Moderate Severe	 56 (78) 10 (14) 0 (0) 6 (8)	N/A	N/A
RDS Deaths	10 (14)	9 (8)	2 (29)
Total Deaths	16 (22)	11 (9)	2 (29)
Survival to Discharge	56 (78)	107 (91)	5 (71)

N/A = Not applicable (as an efficacy outcome)
Cross Reference: Data Listing 5 of Case Report Tabulations (NDA Section XI)

(3) Safety

The complications most frequently reported in the prophylaxis population were PDA (57%), followed by IVH (43%), sepsis (28%), pulmonary hemorrhage (13%) and PVL (11%). In the rescue treatment population, the most frequently reported complication of prematurity was PDA (45%) followed by IVH (23%) and sepsis (18%).

The safety outcomes are difficult to compare with those reported in other clinical studies of Infasurf because of the method used to collect the data. (in the case report form they were entered as "other complications" where some investigators reported some events based on different criteria).

No adverse events were collected or reported as drug-related during its administration.

D. Comments.

This small, open-label, non-randomized, non-controlled trial offered little valid data in efficacy and safety outcomes to be compared with other clinical studies.

4. Protocol 8701/ National Trial of INFASURF Administration at Birth in Premature Infants. Ref Vol. 1.31

A. Study Characteristics and Definitions.

This is an open label, uncontrolled, multicenter (19 centers) trial originally designed to evaluate the safety of Infasurf when used as prophylaxis or for the treatment of RDS. A total of 13,278 infants were enrolled and treated within the study; all were evaluable for efficacy and safety analysis. A total of 9,536 infants were administered Infasurf as a prophylactic treatment and 3,742 infants were given Infasurf in the treatment population.

The primary efficacy endpoints assessed for the prophylaxis population were the incidence of RDS, the incidence of chronic lung disease and the incidence of mortality secondary to RDS. The secondary efficacy endpoints for the prophylaxis population were the incidence of RDS-related air leak syndromes, oxygenation and ventilatory requirements, total mortality, total neonatal mortality, and survival to discharge from the hospital.

In the treatment population, the primary efficacy endpoints were the incidence of RDS-related air leak syndromes, the incidence of chronic lung disease, and mortality secondary to RDS. The secondary efficacy endpoints assessed were oxygenation and ventilatory requirements, total mortality, total neonatal mortality, and total survival to discharge from the hospital.

The dose of Infasurf was: 3 mL /Kg (35 mg of phospholipids/mL suspension). In the prophylaxis arm it was given as a single dose. It could be repeated every 4 hours up to 3 doses, if the patient developed severe RDS. In the treatment arm, Infasurf was given up to three doses if the patient met criteria. Originally, repeat doses were administered at least 12 hours apart. As of 1/11/90 the interval between doses was decreased to 8 hours.

Changes in the definition of Severe RDS:

On 1/26/89 : 70% FiO_2 and MAP ≥12 cm H_20 for $PaO_2 \leq$50-70 torr, and PCO_2 40-55 torr

On 7/13/89: 60% FiO_2, and MAP ≥10 cm H_20 for $PaO_2 \leq$50-70 torr, and PCO_2 40-55 torr

On 9/3/92: $FiO_2 \geq$ 40%, MAP ≥ 8 cm H_2O, and $PaO_2 \leq$ 80 torr or arterial/alveolar $PO_2 \leq$0.33.

The following changes were made to Case Report Forms: four case report forms were utilized during the conduct of the study. After the study was initiated, no CRF changes were submitted to FDA. The four CRF's and the extent of use of each are presented below.

1987 CRF
The Infasurf Patient Report Form 1987 was the most detailed and was completed for 2120 infants who were treated prophylactically with Infasurf. It was to be used for all patients enrolled through April 30, 1988, and is referred to as the "long form" throughout the report.

1988 CRF
Infasurf Report Form 1988 contained the same categories of information as the 1987 CRF, however, demographic information, and respiratory support information were less detailed. CRF's were completed for 1871 prophylaxis patients and 99 treatment patients. This CRF was to be used in the period from May 1, 1988 to February 28, 1989 and is also referred to as the "long form" throughout the report.

1989 CRF
Infasurf Report Form 1989 collected data similar to the 1988 CRF, however, respiratory status following treatment was requested. "Cause of death" was added to the form. CRF's were completed for 2270 prophylaxis patients and 995 treatment patients. This CRF was to be used in the period from March 1, 1989 to January 31, 1990 and is also referred to as the "long form" throughout the report.

1990 CRF
A substantially condensed, two-part CRF was issued in 1990. It was comprised of a Patient Enrollment Log and an Adverse Event / Death Report. This CRF is referred to as the "short form" throughout the report. CRF's were completed for 3275 prophylaxis patients and 2648 treatment patients. The 1990 CRF was to be used in the period from February 1, 1990 through December 31, 1993.

B. Objectives.

Retrospectively, the objective of the study was expanded to assess the effectiveness of Infasurf administration as well as the safety of Infasurf.

C. Results

(1) Efficacy

Prophylaxis Population

A total of 9,536 infants were administered Infasurf for prophylaxis; for 6,261 patients, study data were recorded on the long CRF forms (patients enrolled from 1987 to 1990), and for 3,275 patients, study data were documented on the short CRF form (patients enrolled from 1990 to 1993). The mean birth weight was 1255.5 grams and the mean gestational age was 28.8 weeks.

In the prophylaxis population, 26% of the infants had RDS, defined as the need for ≥ 30% oxygen at 24 hours of age. PIE was reported in 4.3% of the patients, 6.8% had a pneumothorax and 9.1% were noted to have any air leak. RDS and air leaks were recorded only on the long form CRF's.

The incidence of RDS and air leaks was assessed by birth weight and gestational age, (GA) and were noted to be inversely proportional to the birth weight and GA. (TABLES 1 AND 2).

TABLE 1. Incidence of RDS and Air Leaks* by Birth Weight Groups - Prophylaxis Population.

Parameter	< 700 g [N=938]	700 - 1100 g [N=3016]	> 1100 g [N=5553]
RDS	234 (44.2)	628 (35.0)	755 (19.3)
Number	529	1793	3920
PIE	65 (12.5)	118 (6.6)	82 (2.1)
Number	519	1786	3914
Pneumothorax	88 (16.9)	163 (9.1)	168 (4.3)
Number	520	1786	3917
Any Air Leak	122 (23.3)	237 (13.3)	206 (5.3)
Number	524	1786	3919

Number = of patients with available data.
( ) Percentage of patients.
* RDS and air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

TABLE 2. Incidence of RDS and Air Leaks* by Gestational Age Groups - Prophylaxis Population

Parameter	< 29 Weeks (N=4319)	≥ 29 Weeks (N=5201)
RDS	932 (38.2)	688 (18.1)
Number	2439	3811
PIE	206 (8.5)	60 (1.6)
Number	2423	3804
Pneumothorax	278 (11.5)	146 (3.8)
Number	2425	3806
Any Air Leak	390 (16.1)	180 (4.7)
Number	2429	380

Number = of patients with available data.
( ) Percentage of patients.
* RDS and air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 of Case Report Tabulations (NDA Section XI)

Chronic lung disease [bronchopulmonary dysplasia (BPD)] was diagnosed by the attending neonatologist in 1375 (24.2%) of the 5678 prophylaxis patients with data recorded.

Mean airway pressure (MAP) and fraction of inspired oxygen (FiO_2) decreased within 24 hours after Infasurf treatment in the prophylaxis population. A decrease in MAP of almost 5 cm H_2O was noted after 72 hours, and the FiO_2 decreased from over 50% immediately after treatment to less than 30% at 24 hours. Statistically significant changes ($p<0.05$) in both the MAP and FiO_2 from baseline were noted at 24, 48, and 72 hours.

Of the 9536 evaluable patients in the prophylaxis population, 3.0% (290 patients) died of RDS, 7.2% (690 patients) died by Day 7 and 10.2% (974 patients) died by Day 28. Among the evaluable patients in the prophylaxis population, 88% (8395 of 9536) survived to discharge from the hospital. Mortality was inversely proportional to birth weight and GA. TABLE 3 shows the proportion of patients who died during the study at 7 and 28 days, and to discharge.

TABLE 3. Patients Who Died During the Study - Prophylaxis Population

Survival / Death	Prophylaxis Population [N=9536]
RDS Death	290/9536 (3.0)
Death by 7 Days (any cause)	690/9536 (7.2)
Death by 28 Days (any cause)	974/9536 (10.2)
Survival to Discharge	8395/9536 (88.0)

( ) Percentage of patients.
Cross Reference: Data Listing 5 of Case Report Tabulations (NDA Section XI)

Treatment Population

A total of 3,742 infants were administered Infasurf in the treatment population.

The average birth weight in the treatment population was 2,016.1 grams and the average gestational age was 32.4 weeks.

In the treatment population, 15.2% were noted to have PIE, 20.7% had a pneumothorax, and 27.0% were noted to have any air leak syndrome. TABLE 4 shows the incidence of air leaks in the treatment population.

TABLE 4 Incidence of Air Leaks* - Treatment Population

Measured Parameter	Treatment Population [N=3742]
PIE	166/1093 (15.2)
Pneumothorax	226/1093 (20.7)
Any Air Leak	295/1094 (27.0)
BPD	256/1094 (23.4)

Denominator = number of patients with available data
* Air leaks were recorded on long form CRF's only.
Cross Reference: Data Listing 4 and 6 of Case Report Tabulations (NDA Section XI)

BPD was diagnosed by the attending neonatologist in 256 (23.4%) of the babies with data.

In the treatment population, 4.4% (164 of 3742 patients) of the patients died of RDS. Of the 3,742 evaluable patients in the treatment population, 7.1%

(267 patients) died by Day 7 and 10.5% (392 patients) of patients died by Day 28. Among the evaluable patients, 87.8% (3285 of 3742) in the treatment population survived to discharge. The incidence of death due to RDS and death by 7 and 28 days were inversely proportional to the birth weight groups.

(2) Safety:

The most frequently documented complications of prematurity among neonates in the prophylaxis population were: patent ductus arteriosus (PDA) (27.7%), intraventricular hemorrhage (IVH) (19.7%), retinopathy of prematurity (ROP) (17.5%), and sepsis (13.3%). In general, the incidence of complications of prematurity in the birth weight groups and the gestational age groups were inversely proportional to the birth weights and the gestational ages of the neonates. TABLE 6 presents the incidence of complications of prematurity in the prophylaxis population.

TABLE 5. Incidence of Complications of Prematurity - Prophylaxis Population

Parameter	Prophylaxis Population [N=9536]
IVH	1222/6189 (19.7)
IVH Grade I	562/6189 (9.1)
IVH Grade II	188/6189 (3.0)
IVH Grade III	205/6189 (3.3)
IVH Grade IV	254/6189 (4.1)
Pneumonia	462/5020 (9.2)
PDA	1730/6240 (27.7)
Sepsis	830/6224 (13.3)
NEC	431/6223 (6.9)
PVL	106/4001 (2.6)
RLF	84/6069 (1.4)
ROP	1063/6079 (17.5)

Denominator = of patients with available data.
( ) Percentage of Patients
Cross Reference: Data Listing 3 of Case Report Tabulations (NDA Section XI)

Of the 9,536 patients evaluable, 1,141 infants (12.0%) had died prior to discharge from the hospital. The most frequently reported cause of death was RDS (3.0%) followed by bacterial infection and septicemia (1.5%), lung hypoplasia syndromes (1.2%), NEC (1.0%), renal failure (0.9%), and chronic lung disease (0.9%).

The most frequently documented complications of prematurity in the treatment population were: PDA (38.5%), IVH (21.7%), pneumonia (17.2%), and sepsis (15.6%). In general, the incidence of adverse events in the birth weight groups and the gestational age groups were inversely proportional to the birth weights of the infants and the gestational ages.

TABLE 6. Incidence of Complications of Prematurity - Treatment Population

Parameter	Treatment Population [N=3742]
IVH	232/1070 (21.7)
IVH Grade I	68/1070 (6.4)
IVH Grade II	45/1070 (4.2)
IVH Grade III	54/1070 (5.0)
IVH Grade IV	53/1070 (5.0)
Pulmonary Hemorrhage	45/1093 (4.1)
Pneumonia	69/402 (17.2)
PDA	420/1091 (38.5)
Sepsis	170/1091 (15.6)
NEC	29/1092 (2.7)
PVL	29/1060 (2.7)
RLF	18/1058 (1.7)
ROP	101/1059 (9.5)

Number = Number of patients with available data.
( ) Percentage of Patients
Cross Reference: Data Listing 3 of Case Report Tabulations (NDA Section XI)

Of the 3742 patients in the treatment population evaluable for safety at the time of discharge, 12.2% (457 patients) had died prior to discharge. The most frequently reported cause of death was RDS (4.4%) followed by bacterial infection and sepsis (1.7%), chronic lung disease (1.4%), and lung hypoplasia syndromes (1.0%).

Patients Who Died:

Prophylaxis Population
Of the 9,536 patients in the prophylaxis population evaluable for safety, 1,141 patients (12.0%) died prior to discharge and 290 patients (3.0%) died due to RDS.

The most frequently reported cause of death was RDS (3.0%) followed by bacterial infection and septicemia (1.5%), lung hypoplasia syndromes (1.2%), NEC (1.0%), renal failure (0.9%), and chronic lung disease (0.9%).

Treatment Population
In the treatment population, 457 patients (12.2%) died prior to discharge and 164 (4.4%) of the patients died due to RDS.

The most frequently reported cause of death was RDS (4.4%) followed by bacterial infection and septicemia (1.7%), chronic lung disease (1.4%), and lung hypoplasia syndromes (1.0%).

C. **Comment**

The meaning of the results of this large, open label, non randomized, non-controlled study are further complicated by a series of changes made in the definition of some of the primary endpoints and entry criteria, and on the CRF's for the collection of data through the years that the study was conducted. Several of the variables measured were not objectively defined. Some of the necessary diagnostic procedures and tests to better define the variables studied, e.g., CXR's, sonograms, were later on left up to the individual investigator, following the standard of care of each center. The latter makes variables like incidence and severity of RDS, incidence of IVH, incidence of air leaks and even RDS death impossible to define across the centers and along the years that the study lasted. The incidence of adverse events during administration of the surfactant was not addressed uniformly,